FOUR-YEAR STUDY OF ENTECAVIR EFFICACY AND SAFETY IN NUCLEOS(T)IDE-NAÏVE HBeAg POSITIVE CHRONIC HEPATITIS B PATIENTS

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SUMMARY – Entecavir is a guanosine analogue with activity against hepatitis B virus. The aim of this 4-year trial was to evaluate entecavir treatment in nucleos(t)ide-naïve HBeAg-positive chronic hepatitis B patients. Forty-nine patients received entecavir and nine of them withdrew from the trial at the end of week 96. The initial mean value of alanine aminotransferase was 79.4±41.5 IU/L, and at the end of the 4-year study period, 90% of patients had alanine aminotransferase values within the normal range. At week 96, 91.7% of patients had HBV DNA <300 copies; at month 48, 90% of patients had HBV DNA <50 IU/mL. HBeAg loss was recorded in 7.1% of patients at week 96 and in 12.5% at month 48. The rate of HBeAg seroconversion was 4.8% at week 96 and 7.5% at month 48. The rate of HBsAg seroconversion was 2.1% at week 96 and 2.5% at month 48. Entecavir as a potent and safe agent leading to continuous viral suppression proved to be safe and well tolerated therapy.

Key words: *Guanine – therapeutic use; Hepatitis B, chronic; Antiviral agents – therapy*

Introduction

Chronic hepatitis B (CHB) infection is a major health problem caused by hepatitis B virus (HBV). CHB infection can lead to liver failure, liver cirrhosis (LC) and hepatocellular carcinoma (HCC), and affects over 350 million people worldwide. HBV has a covalent closed circular DNA (cccDNA), which is the cause of the sustainability of the HBV. Elimination of HBV is very difficult and the main purpose of therapy is to sustain viral suppression. Antiviral drugs that are used in the treatment of CHB include interferon [interferon-alpha (IFN-α) and pegylated (PEG) IFN-α] and nucleosides or nucleoside analogues [entecavir (ETV), adefovir dipivoxil (ADV), telbivudine (LdT, β-L-2'-deoxythymidine), and lamivudine (LAM)]. Nucleos(t)ide analogues (NA) target the reverse transcriptase of HBV. This group of drugs are potent inhibitors of viral replication. Studies have shown that continued therapy with NA can suppress viral replication over prolonged periods, and can result in delay or even prevention of clinical progression to liver cirrhosis and hepatocellular carcinoma. However, antiviral drug resistance limits the efficacy of these drugs[1]. Among nucleoside analogues, ETV is a strong new-generation nucleoside analogue. According to literature data, ETV proved advantageous for a higher rate of HBV DNA suppression and low drug-resistance[2]. However, in the literature, there is a limited number of studies evaluating the efficacy and safety of entecavir treatment in HBeAg positive naïve

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CHB over a long period. For this reason, we aimed to assess the long-term, 4-year efficacy and safety of entecavir treatment in nucleos(t)ide-naïve HBeAg-positive CHB patients with various baseline data.

Material and Methods

This multicenter study was conducted in the southeast part of Anatolia, Turkey (Diyarbakir, Batman, Kiziltepe and Midyat). The study included 49 naïve HBeAg-positive CHB patients who had never taken nucleos(t)ide treatment, aged 22-60 years, treated with entecavir (0.5 mg/day) for 96 weeks and followed between 2007 and 2011 at the Infectious Disease Department, Dicle University Hosital, Diyarbakır Private German Hospital, Batman State Hospital and Midyat State Hospital. Serum HBV DNA level, alanine aminotransferase (ALT) activity, HBeAg, anti-HBe-antibodies, HBsAg, anti-HBs, HBV DNA level, creatinine level, and urea level were evaluated at baseline, and at weeks 12, 24, 48 and 96 during therapy. At the end of week 96, nine patients did not present for follow up examination and were excluded. The remaining 40 patients continued presenting for follow up and continued to receive 0.5 mg/day entecavir therapy throughout the 4-year period. In the remaining 40 patients, serum ALT activity, HBeAg, anti-HBe-antibodies, HBsAg, anti-HBs, HBV DNA level, creatinine level and urea level were investigated and evaluated at month 36 (3 years) and month 48 (4 years).

In this study, the diagnosis of naïve HBeAg positive CHB was based on HBsAg positivity, HBeAg positivity, HBV DNA >10^5 copies/mL, ultrasonography findings, and liver biopsy, as follows: 1) seropositive for HBsAg, serum ALT elevation for at least 6 months (normal range: 13-31 U/L for females and 13-53 U/L for males), and detectable serum HBV DNA; 2) no evidence for hepatocellular carcinoma, hepatitis C virus, human immunodeficiency virus or hepatitis D virus infection; and 3) creatinine clearance of more than 70 mL *per* minute. Liver biopsy was performed within 6 months of entry. Liver histology was analyzed according to the criteria of Ishak (comprising two major components: necroinflammation and fibrosis). Patients were excluded from the study if they had previously received nucleos(t)ide analogue or interferon-alfa therapy[3].

Hepatitis B surface antigen (HBsAg), HBeAg and hepatitis B e antibody (anti-HBe) (Abbott Laboratories, North Chicago, IL, USA) were assayed with the fourth generation enzyme linked immunosorbent assay. All patients underwent blood testing for liver biochemistry (ALT, AST, ALP, GGT, albumin, and bilirubin), complete blood count, prothrombin time, and renal biochemistry before commencement of therapy. Serum HBV-DNA was measured by the TaqMan polymerase chain reaction assay (TaqMan HBV Assay, Roche Diagnostics; lower limit of quantification = 35 copies/mL).

Statistical analyses were performed with the Statistical Package for Social Sciences version 15.0 software (Friedman and Cochran Q tests). Values of p less than 0.05 were considered significant.

Results

Results in 49 patients treated with entecavir (0.5 mg/day) for 96 weeks

The patient mean age was 38.8±10.2 years. The initial mean value of ALT was 79.4±41.5 IU/L. At baseline, the mean fibrosis score (Ishak) of liver biopsy was 2.27±0.75. Overall, 49 HBeAg positive patients completed treatment week 96. At treatment weeks 12, 48 and 96, HBV DNA <300 copies were recorded in 8.2%, 89.8% and 91.7% of patients, respectively. At treatment week 96, HBeAg loss was observed in 7.1%, HBeAg seroconversion in 4.8% and HBsAg seroconversion in 2.1% of patients. At week 96, the mean ALT level was 32.6 IU/L, showing significant decrease as compared with the initial ALT level (Table 1). Treatment safety was good. None of the patients had a confirmed creatinine increase of 0.5 mg/dL. Renal safety was good. Creatinine remained stable throughout the 96-week trial.

Results in 40 patients having continued follow up and treatment with entecavir (0.5 mg/day) for 4 years

Among the patients that continued presenting for follow up, 92.5% achieved HBV DNA <50 IU/mL at month 36 and 90% at month 48 of treatment. HBeAg loss was observed in 10% of patients at month 36 and 12.5% at month 48. HBeAg seroconversion was observed in 5% of patients at month 36 and 7.5% at month 48. HBsAg loss was observed in 2.5% of

patients at month 36 and 5% at month 48. HBsAg seroconversion was recorded in 2.5% patients at month 36 and 2.5% at month 48. In 92.5% of the 40 patients, ALT values were within the normal range at the end of the third year and in 90% at the end of the fourth year. At the end of the fourth year, treatment safety was good. None of the patients had a confirmed creatinine increase of 0.5 mg/dL, and renal safety was good.

Discussion

Nucleos(t)ide analogues (NA) are potent inhibitors of viral replication. Continued therapy with NA can suppress viral replication over prolonged periods. Suppression of viral replication causes delay or prevention of clinical progression to liver cirrhosis and hepatocellular carcinoma. However, antiviral drug resistance is a major problem in antiviral-therapy of HBV infection due to the limited efficacy of these drugs[1].

According to European guidelines, partial virologic response (PVR) is defined as a >1 log IU/mL decline in HBV DNA from baseline but a detectable load at week 24 or week 48[4].

Entecavir is a strong new generation nucleoside analogue[4]. In the literature, there are a limited number of studies evaluating the efficacy and safety of ETV treatment in HBeAg positive naïve CHB patients for a long period. For this reason, we believe that our study, which investigated the 4-year (48 months) long-term efficacy and safety of entecavir treatment in nucleos(t)ide-naïve HBeAg-positive CHB patients, will contribute to clarifying the issue and can serve as a guide for the long-term treatment approach to nucleos(t)ide-naïve HBeAg-positive CHB patients.

To our knowledge, HBV DNA level is a primary prognostic marker for the treatment of patients with CHB. The early and sustained suppression of HBV DNA replication leads to improved long-term rates of virologic, serologic and biochemical responses. Rapidly and effectively suppressing HBV DNA replication can decrease the incidence of LC, HCC and drug resistance[2]. In our study, 8.2% of nucleos(t)ide-naïve HBeAg-positive CHB patients achieved HBV DNA <300 copies at week 12 of treatment, 89.8% at week 48, and 91.7% at week 96. Our study showed that with ETV, the great majority of nucleos(t)ide-naïve HBeAg-positive CHB patients achieved HBV DNA <300 copies at week 48. In addition, we observed that 92.5% of patients having continued presenting for follow up achieved HBV DNA <50 IU/mL at month 36 and 90% at month 48 of treatment. Based on our results, we suggest that ETV is an efficacious agent suppressing HBV DNA replication for a long period. On the other hand, studies demonstrated that clearance of HBsAg was related to very low or undetectable HBV DNA [<300 copies/mL], normalization of serum ALT levels, improvement in liver histology, a decreased risk of HCC, and prolonged survival[5,6]. In some long-term natural history studies, it was estimated that the rate of spontaneous HBsAg seroclearance was 0.5%-1.7% *per* year[7-10]. According to the literature, HBsAg seroclearance was observed less frequently in Asian patients (<1%/year), who typically acquire HBV at birth, than in western patients who mainly gain HBV later in life[5,11]. In a retrospective study of nucleoside-naïve hepatitis B e antigen (HBeAg)-positive CHB patients who achieved hepatitis B surface antigen (HBsAg) loss during ETV or LAM therapy for maximum duration of 96 weeks on-treatment and 24 weeks off-treatment, HBsAg loss was confirmed in 5.1% of patients treated with ETV and 2.8% of patients treated with LAM. Among patients with HBsAg loss, 96% achieved HBV DNA <300 copies/mL, and 96% achieved HBeAg loss. This retrospective study revealed that HBsAg loss was related to sustained off-treatment suppression of HBV DNA[12]. In addition, HBeAg is a protein expressed by pre-C gene and HBeAg is lost with the rise of immunomodulatory effect, which can suppress HBV DNA replication. HBeAg seroconversion is considered to be a marker of treatment response and to be related with improved clinical outcomes. It is one of the important withdrawal signs for HBeAg-positive patients and it is suggested that patients with HBeAg seroconversion can achieve sustained immune response[2]. In our study, HBsAg seroconversion was observed in 2.1% of patients on treatment at week 96 and in 5% on treatment at month 48. Furthermore, we observed HBeAg loss in 7.1% of patients on treatment at week 96 and in 12.5% on treatment at month 48. In our country, genotype D is the predominant genotype among patients with hepatitis B and it is known that CHB patients with genotype D have poor response to treatment.

Table 1. Results of entecavir treatment at week 96

		Week 96 HBV DNA <300 copies/mL			HBe Ag loss		
		n	%	p	n	%	p
Age (yrs)	<40	28	100.0	0.025	3	10.7	0.255
	≥40	16	80.0		0	0.0	
Gender	Female	18	90.0	1.000	3	15.0	0.066
	Male	26	92.9		0	0.0	
Fibrosis	<3	26	86.7	0.290	2	6.7	1.000
	≥3	14	100.0		1	7.1	
HAI	<7	26	92.9	0.614	1	3.6	0.543
	≥7	14	87.5		2	12.5	
Baseline ALT	<70	11	73.3	0.007	0	0.0	0.542
	>70	33	100.0		3	9.1	

AI = histology activity index; ALT = alanine aminotransferase

We presumed that low HBsAg seroconversion rates and HBeAg loss rates in our study were related to the predominant genotype in Turkey.

In the literature, there are reports on some studies evaluating the efficacy and safety of ETV treatment in HBeAg positive NA-experienced patients with CHB; however, there are a limited number of studies investigating ETV as long-term monotherapy in NA-naïve patients.

Reijnders *et al*. investigated 161 CHB patients (34% NA-experienced) treated with ETV monotherapy. They found that 79% of NA-naïve patients achieved virologic response during a median follow up of 11 months and 54% of NA-experienced patients during a median follow up of 12 months. They showed ETV to be an efficacious drug in NA-naïve patients. They also demonstrated that the antiviral efficacy of ETV was not influenced by prior treatment with ADV but that ETV should not be used in patients with previous LAM-resistance[1]. Sherman *et al*. also showed that antiviral efficacy of ETV was significantly decreased in patients with LAM-resistant mutations at the start of ETV monotherapy[13].

Jiyang *et al*. analyzed ETV-treated and ADV-treated CHB patients. They found that the negative rate of HBeAg seroconversion was significantly increased at 24 weeks in ETV-treated patients, whereas in ADV-treated patients, these changes were not significant. According to their study, ETV showed significantly decreased levels of HBV DNA at 24 weeks when compared with ADV; there was no difference in virologic response between the two treatments at any other time point. The ALT and total bilirubin levels were significantly decreased at 12 weeks in both ETV-treated and ADV-treated patients without differences between the two treatments[14].

Leung *et al*. found that the mean decrease in serum HBV DNA and the proportion of patients achieving HBV DNA less than 300 copies/mL were greater in ETV-treated than ADV-treated patients at weeks 2, 4, 8, 12, 24 and 48. At week 48, 3% of ETV-treated *versus* 47% of ADV-treated patients had HBV DNA of 10^5 copies/mL or more, and they suggest that ETV therapy resulted in earlier and superior reduction in HBV DNA compared with ADV in nucleoside-naïve HBeAg-positive CHB patients[15]. In their 96-week study, Gish *et al*. found that 74% of ETV-treated *versus* 37% of LAM-treated patients achieved HBV DNA <300 copies/mL, and 79% of ETV-treated *versus* 68% of LAM-treated patients had normalized ALT levels. Similar proportions of ETV-treated and LAM-treated patients achieved HBeAg seroconversion (11% *vs*. 12%)[16].

All of these comparative studies have shown that entecavir has superiority when compared to many known drugs used in the treatment of NA-naïve CHB patients. Recent studies have shown that LdT is the strongest oral bioavailable nucleoside analogue. It can effectively suppress HBV DNA replication, and has a higher rate of hepatitis B e antigen (HBeAg) seroconversion than other current oral antiviral agents[17]. However, studies have shown that its drug-resistance

remains high. In a comparative study of EBV and LdT, Su *et al*. found that at 4 weeks and 8 weeks of treatment, the rates of HBeAg loss and HBeAg seroconversion were similar for EBV and LdT, while at weeks 12, 24, 48 and 52, the rate was higher in the LdT group than in the ETV group. However, at weeks 60 and 72, there was no significant difference in the rate of HBeAg seroconversion between the two groups in their study. In addition, between week 4 and week 72, there were no statistical differences in the rate of ALT normalization between the two groups[3]. According to literature data, it appears that drug resistance of LdT limits its use in long-term therapy, but ETV can be used for a long period in patients with NA-naïve CHB[3].

In a multicenter cohort study, it was observed that virologic response (HBV DNA <80 IU/mL) was achieved in 48%, 76% and 90% of HBeAg-positive, and in 89%, 98% and 99% of HBeAg-negative NA-naïve patients at weeks 48, 96 and 144, respectively; 21% of NA-naïve patients with at least 48-week follow up had a detectable load at week 48 (partial virologic response); 81% of patients with partial virologic response reached virologic response during prolonged ETV monotherapy, and none of them developed ETV-resistance. They found that ETV was safe and did not affect renal function or cause lactic acidosis; the authors suggest that ETV monotherapy can be continued in NA-naïve patients with detectable HBV DNA at week 48, particularly in those with a low viral load because long-term ETV leads to virologic response in the vast majority of patients[3]. Chang *et al*. also report that extended therapy with ETV for 5 years maintained or increased the rates of HBV DNA suppression and ALT normalization. Additional patients also achieved HBeAg loss and seroconversion. Entecavir provided sustained viral suppression with minimal resistance during long-term treatment of HBeAg positive CHB patients[18].

In addition, we observed that the mean values of ALT as an indicator of therapeutic response declined during therapy and creatinine remained stable. According to our results on HBsAg loss, HBaAg seroconversion, HBeAg loss and HBeAg seroconversion, we can say that in short-term treatment of CHB, ETV was not superior, but based on our long-term results ETV could be used in long-term treatment of nucleoside-naïve CHB patients. Entecavir had a high genetic barrier to resistance and proved to be a safe agent.

In conclusion, the results of this long-term study of ETV showed that among HBeAg-positive patients, therapy with ETV for 4 years achieved and maintained high rates of HBV DNA suppression and normal ALT levels. Entecavir was also well tolerated throughout the 4-year administration. With its safety, viral suppression, and resistance profile, ETV is now considered a preferred choice for long-term treatment of nucleoside-naïve HBeAg-positive CHB patients.

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Sažetak

ČETVEROGODIŠNJA STUDIJA UČINKOVITOSTI I SIGURNOSTI ENTEKAVIRA U BOLESNIKA S KRONIČNIM HEPATITISOM B POZITIVNIH NA HBeAg BEZ PRETHODNE NUKLEOZ(T)IDNE TERAPIJE

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Entekavir je analog gvanozina koji djeluje protiv virusa hepatitisa B. Cilj ove četverogodišnje studije bio je procijeniti liječenje entekavirom kod bolesnika s kroničnim hepatitisom B pozitivnih na HBeAg bez prethodne nukleoz(t)idne terapije. Ukupno je 49 bolesnika primalo entekavir, a devetoro ih se povuklo s terapije na kraju 96. tjedna. Početna srednja vrijednost alanin aminotransferaze bila 79,4±41,5 IU/L, dok je nakon 4 godine vrijednost alanin aminotransferaze bila u normalnim granicama kod 90% bolesnika. U 96. tjednu je <300 kopija HBV DNA zabilježeno u 91,7% bolesnika, a u 48. mjesecu je 48,90% bolesnika imalo <50 IJ/mL HBV DNA. Gubitak HBeAg zabilježen je u 7,1% bolesnika u 96. tjednu te u 12,5% bolesnika u 48. mjesecu. Stopa serokonverzije HBeAg iznosila je 4,8% u 96. tjednu i 7,5% u 48. mjesecu. Stopa serokonverzije HBsAg bila je 2,1% u 96. tjednu i 2,5% u 48. mjesecu. Sigurnost terapije bila je dobra. Bolesnici su dobro podnosili entekavir, snažan i siguran lijek koji dovodi do ustaljenog suzbijanja virusa.

Ključne riječi: *Ganin – terapijska primjena; Hepatitis B, kronični; Antivirusni lijekovi – terapija*